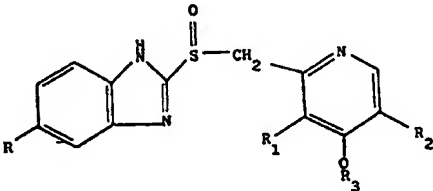
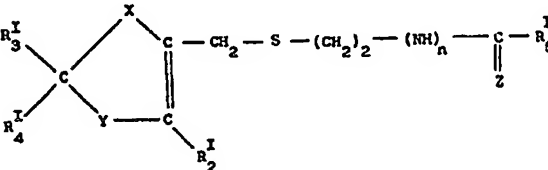
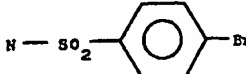




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C07D 401/12, 233/61, 307/52, 277/28, 277/48, A61K 31/44, 31/415, 31/34, 31/425</p>	<p>A1</p>	<p>(11) International Publication Number: WO 99/45004 (43) International Publication Date: 10 September 1999 (10.09.99)</p>
<p>(21) International Application Number: PCT/EP99/01226 (22) International Filing Date: 25 February 1999 (25.02.99) (30) Priority Data: MI98A000442 5 March 1998 (05.03.98) IT (71) Applicant (for all designated States except US): NICOX S.A. [FR/FR]; 45, avenue Kléber, F-75116 Paris (FR). (72) Inventor; and (75) Inventor/Applicant (for US only): DEL SOLDATO, Piero [IT/IT]; Via Toti, 22, I-20052 Monza (IT). (74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni, 2, I-20129 Milano (IT).</p>		<p>(81) Designated States: AL, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.</p>
<p>(54) Title: NITRATE SALT OF ANTI-ULCER MEDICINE</p> <div style="text-align: center;">  <p>(A)</p> </div> <div style="text-align: center;">  <p>(B)</p> </div> <div style="text-align: center;">  <p>(VIIA)</p> </div>		
<p>(57) Abstract</p> <p>Nitrate salt compositions with anti-ulcer medicines having formula (A) and (B) wherein the (A) class compounds: R = H, OCH₃, OCHF₂; R₁ = CH₃, OCH₃; R₂ = H, CH₃; R₃ = CH₃, CH₂-CF₃, (CH₂)₃-OCH₃; wherein the (B) class compounds: R¹₃, R¹₄ equal to or different from each other, are respectively free valence hydrogen, (1), -CH₂-N(CH₃)₂; Y = S, N-R¹₆, CR¹₇R¹₈; X = O, S, N-R¹₁; R¹₂ = H, CH₃; n = 0, 1; Z = N-CN, N-SO₂NH₂, CH-NO₂ or formula (VIIA) R¹₅ = H, -NH-CH₃, NH₂; R¹₆, R¹₇, R¹₈, R¹₁, equal to or different from each other, are hydrogen, free valence. The invention also comprises the methods for the preparation of above salts.</p>		

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

"NITRATE SALT OF ANTI-ULCER MEDICINE"

* * * * *

The present invention relates to compositions to be used in the therapy and in the prevention of the ulcer relapses and, in general, of dyspepsias. More particularly it relates to compositions having an improved gastroprotective activity combined with a high acid secretion inhibition activity.

Products known in the art and those commercialized and used in the ulcer therapy are compounds which perform an anti-secretory activity (acid secretion inhibition). See for instance " New Guide to Medicine & Drugs" Brit. Medical Assoc. Editor, 1997, pagg. 108-109. Known products having higher therapeutic efficacy show a high anti-secretory activity and are used, both in the acute and in long-term (six months and more) therapies. The drawback of these products is that they have a poor gastroprotective activity, when present. From a practical point of view this means that the gastric protection is not optimal and causes inconveniences above all in the long-term therapy. In this case the presence of frequent relapses due to the enfeeblement of gastric mucosa is noticed.

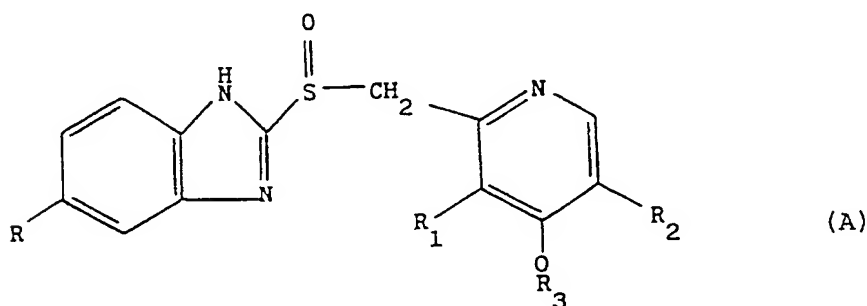
To overcome these inconveniences it is known in the art to add to above medicines other anti-ulcer medicines having a gastroprotective action: prostaglandins, bismuth salts (e.g.

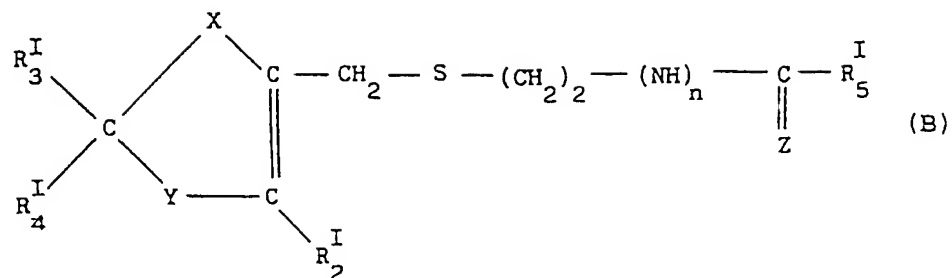
bismuth citrate) and antibiotics. In such way the remission of ulcerous pathology is achieved. However above combinations are not satisfactory as for their tolerability in general. For example it is well known that prostaglandins produce side effects (diarrhoea) towards the intestinal tract; bismuth salts frequently produce nausea and gastric burning. Antibiotics produce unwanted gastrointestinal effects.

The need was felt to have available compositions active in the ulcer and gastric dyspepsia treatment, having improved therapeutic characteristic and tolerability, general and local, in particular having an improved gastroprotective activity combined to a high anti-secretion activity.

The Applicant has unexpectedly and surprisingly found pharmaceutical anti-ulcer compositions having the above mentioned desired properties.

It is an object of the present invention pharmaceutical compositions comprising as essential components nitrate salts of one or more components selected from the following classes of compounds:





where in the (A) class compounds:

$R = H, OCH_3, OCHF_2;$

$R_1 = CH_3, OCH_3;$

$R_2 = H, CH_3;$

$R_3 = CH_3, CH_2-CF_3, (CH_2)_3-OCH_3;$

where in the class (B) compounds:

R_3^I, R_4^I equal to or different from each other, are respectively free valence, hydrogen $-N=C(NH_2)_2$, $-CH_2-N(CH_3)_2$;

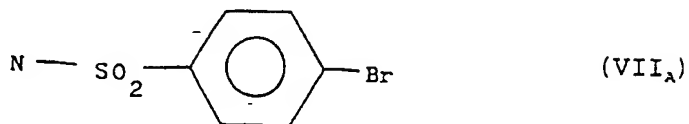
$Y = S, N-R_6^I, CR_7^I R_8^I;$

$X = O, S, N-R_1^I;$

$R_2^I = H, CH_3;$

$n = 0, 1;$

$Z = N-CN, N-SO_2NH_2, CH-NO_2$ or



$R_5^I = H, -NH-CH_3, NH_2;$

$R_6^I, R_7^I, R_8^I, R_1^I$, equal to or different from each other, are hydrogen, free valence.

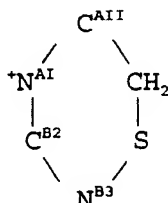
The preferred nitrate salts with the (A) formula precursors are the following:

when $R = OCH_3$, $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = CH_3$, Omeprazole residue; as in Omeprazole, but with $R = OCHF_2$, $R_1 = OCH_3$, $R_2 = H$, Pantoprazole residue;

as in Omeprazole, but with $R = H$, $R_2 = H$, $R_3 = (CH_2)_3-OCH_3$, Rabeprazole residue;

as in Rabeprazole, but with $R_3 = CH_2-CF_3$, Lansoprazole residue.

In the (A) class compounds also those having the following intramolecular ring are comprised, obtainable by treating the precursors in an acid aqueous environment (rif. "A Textbook of Drug Design and Development", Harwood Academic Publisher, 1991, pag. 140):



wherein N^{AI} and C^{AII} mean, respectively, the nitrogen and carbon atom in 1 and 2 position of the pyridine ring of formula A and C^{B2} and N^{B3} the carbon and nitrogen atom, respectively, in 2 and 3 position of the imidazole ring (1 position of the imidazole ring is that of the proton nitrogen).

The preferred nitrate salts with the (B) formula precursors are the following:

when in (B) formula $X = N-R^I_1$ with R^I_1 free valence, $Y = N-R^I_6$ with $R^I_6 = H$, $R^I_3 = H$, R^I_4 is a free valence and forms with R^I_1 ,

a double bond, $R^I_2 = CH_3$, $n = 1$, $R^I_5 = -NH-CH_3$, $Z = N-CN$, Cimetidine residue;

when $X = N-R^I_1$ with R^I_1 free valence, $Y = S$,

$R^I_3 = -N \equiv C(NH_2)_2$, R^I_4 is a free valence and forms with R^I_1 a double bond, $R^I_2 = H$, $n = 1$, $R^I_5 = H$, $Z = (VII_A)$, Ebrotidine residue;

as in Ebrotidine but with $n = 0$, $R^I_5 = NH_2$ and $Z = N-SO_2NH_2$, Famotidine residue ;

as in Ebrotidine but with $R^I_3 = -CH_2-N(CH_3)_2$, $R^I_5 = -NH-CH_3$ and $Z = CH-NO_2$, Nizatidine residue;

as in Nizatidine, but with $X = \text{oxygen}$, $Y = CR^I_7R^I_8$ with R^I_7 hydrogen and R^I_8 free valence, R^I_4 is a free valence and forms with R^I_8 a double bond, Ranitidine residue.

In the compositions according to the present invention also isomers of the compounds belonging to (A) and (B) classes may be used.

In the compositions according to the present invention the compound salts of above classes contain at least one mole of nitrate ion/mole of compounds. Preferably the ratio between the nitrate ion moles and the precursor is equal to one. Salts having a higher molar ratio are obtained when in the molecule other amino groups basic enough to be salified are present.

Salt precursors belonging to the above mentioned classes are prepared according to the methods described in "The Merck Index 12th Ed." (1996), herein completely incorporated by reference.

The salts of the present invention may be prepared accor-

ding to one of the following methods.

When the substance to be salified is available as free base or as a soluble corresponding salt in an organic solvent, which preferably does not contain hydroxyl groups, for example acetonitrile, ethyl acetate, tetrahydrofuran ecc., the salt is prepared by dissolving the substance in the solvent at a concentration preferably equal or higher than 10% w/v, by adding the amount of concentrated nitric acid corresponding to the moles of salifiable aminic groups present in the compound. The nitric acid is preferably diluted in the same solvent. Preferably during and after the addition the mixture is cooled to temperatures in the range 20°-0°C. The product is generally recovered by filtration and washed with the solvent.

When on the contrary the substance is not much soluble or it is available as a not much soluble salt in the above mentioned solvents, the corresponding mixtures with hydroxylated solvents may be used. Examples of such solvents are methyl alcohol, ethyl alcohol and water. The precipitation can be quickened by diluting then the so obtained mixture, after the addition of nitric acid, with an apolar solvent.

When the starting product is salified with hydrochloric acid it is possible to prepare the salt with nitric acid directing adding silver nitrate to the compound solution. After filtering silver chloride, the solution is concentrated and cooled to recover the nitrate salt.

When the starting product is a salt, it is possible to liberate the corresponding base by a treatment with a sodium

or potassium carbonate or bicarbonate saturated solution, or with a sodium or potassium hydroxide diluted solution. The base is then extracted by a suitable organic solvent (e.g. halogenated solvents, esters, ethers) which is then dried. The organic solution is evaporated and then one proceeds according to the preceding preparation methods, by dissolving the base in acetonitrile or in the other above mentioned solvents.

It has now surprisingly been found that the compositions of the present invention allow to improve, compared with the known above mentioned combinations, the comprehensive pharmacotoxicological situation of precursors, increasing the therapeutic efficacy and their general and local tolerability in the ulcer and gastric dyspepsia treatment with an improved gastroprotective activity.

The compositions of the present invention are formulated in the corresponding pharmaceutical compositions according to well known techniques in this field together with the common excipients; see for example the volume "Remington's Pharmaceutical Sciences 15a Ed."

The invention salt dosages are the conventional ones of their precursors of (A) and (B) classes.

It is a further object of the present invention the compositions obtainable combining one or more nitrate salts of the compounds of (A) and (B) classes, or their pharmaceutical compositions, with conventional gastroprotectives. As examples, prostaglandines, bismuth salts, active antibiotics towards pathogenic microorganisms in the gastrointestinal mucosa

can be mentioned. It has surprisingly been found that gastro-protective activity of the invention compositions is very high. This makes it possible to avoid the undesirable effects of known gastroprotectives when they are used in combination with compounds or formulation of the invention. It has indeed been found that the amount of known gastroprotectives, in the combination of the invention, is lower compared with those known and does not cause undesirable effects. The skilled in this field is able to easily determine the maximum amount of conventional gastroprotectives to be combined with the pharmaceutical compositions of the invention since this corresponds to the absence of typical side effects of known gastroprotectives. In any case the amount of conventional gastroprotectives to be used in the combination is lower than that used in the combinations described in the art.

The following examples have the purpose to illustrate the invention and must not be considered as limitative of the same.

EXAMPLE 1

Preparation of cimetidine nitrate salt.

10 g of cimetidine are dissolved in 100 ml of an acetonitrile/tetrahydrofuran/water 1 : 1 : 2 (composition by volume) mixture cooled at +4°C. 10 ml acetonitrile solution containing 2.5 ml of 70% nitric acid are added little by little. The solution is diluted with ethyl ether, maintaining the temperature at +4°C, till to incipient precipitation of the product.

After a some hour rest the precipitated solid is filtered, washed with ethyl ether and dried. 12.1 g of cimetidine mononitrate salt are recovered having m.p. 158°-159°C (with decomposition).

¹H-NMR (D₂O): 8,55 (1H, s), 3,83 (2H, s), 3,32 (2H, s), 2,77 (3H, s), 2,68 (2H, t), 2,32 (3H, s).

Elementary analysis:

calc. (%)	C 38,09	H 5,43	N 31,09	S 10,17
found (%)	C 37,99	H 5,41	N 31,16	S 10,25

EXAMPLE 2

Preparation of ranitidine nitrate salt.

5 g of ranitidine hydrochloride are dissolved in a 140 ml acetonitrile/methyl alcohol 6 : 1 mixture at + 20°C. 4,2 g of powder silver nitrate are added. The silver chloride precipitate is filtered, the precipitate is washed with an acetonitrile/methyl alcohol 6 : 1 solution, the organic phases are put together, dried and treated to obtain a dry residue. 3,5 g of an amorphous solid corresponding to the ranitidine mononitrate salt are obtained.

¹H-NMR (D₂O) : 6,70 (1H, d), 6,40 (1H, d), 4,34 (2H, s), 3,83 (2H, s), 3,43 (2H, t), 2,93 (2H, m), 2,87 (9H, s).

calc. (%)	C 41,37	H 6,14	N 18,56	S 8,50
found (%)	C 41,12	H 6,20	N 18,44	S 8,38

PHARMACOLOGICAL TESTS

EXAMPLE 3

Acute Toxicity

A single dose equal to 100 mg/Kg respectively of cimeti-

dine and ranitidine nitrate salts, dealt with in the previous Examples, has been given to a group of 10 rats weighing 20 g each by a cannula by oral way in a carboxymethylcellulose aqueous suspension 2% w/v.

The animals are kept under observation for 14 days. In no one of the group animals the toxic symptom presence was noted.

EXAMPLE 4

Anti-ulcer Activity

Anti-ulcer activity is evaluated according to the experimental model described in the paper of A. Robert et al.

"Cytoprotection by prostaglandins in rats. Prevention of gastric necrosis produced by alcohol, HCl, NaOH, hypertonic NaCl and thermal injury" Gastroenterology 77, 433-43 1979.

To 5 groups of 10 rats each, kept on empty stomach since the previous night, 15 minutes before the supply of absolute ethyl alcohol (1 ml), by oral way are supplied:

- 5 ml/Kg of carboxymethylcellulose aqueous suspension 2%.
- 50 mg/Kg of cimetidine in 5 ml/Kg of carboxymethylcellulose aqueous suspension 2%.
- 62,5 mg/Kg of cimetidine nitrate (corresponding to 50 mg/Kg of cimetidine) in 5 ml/Kg of carboxymethylcellulose aqueous suspension 2%.
- 50 mg/Kg of ranitidine in 5 ml/Kg of carboxymethylcellulose aqueous suspension 2%.
- 60 mg/Kg of ranitidine nitrate (corresponding to 60 mg/Kg of ranitidine) in 5 ml/Kg of carboxymethylcellulose aqueous suspension 2%.

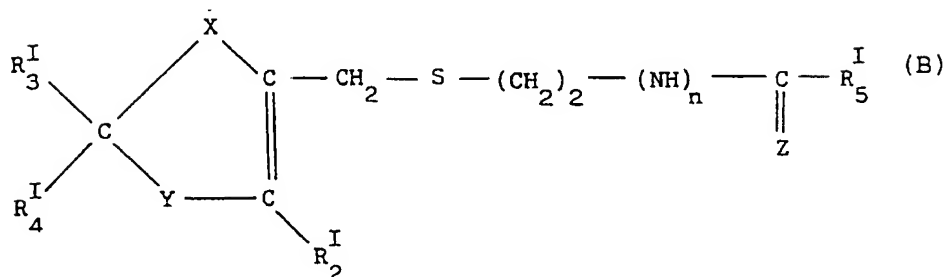
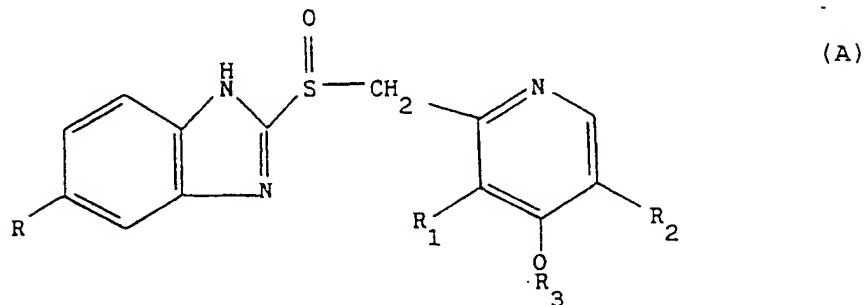
A hour later the animals are sacrificed and the gastric lesion incidence is evaluated. Results are reported in Table 1 and they show that cimetidine and ranitidine nitrate salts have an improved gastroprotective activity compared with the corresponding starting products.

TABLE I

Treatment	Gastric Damage (%)
Vehicle	100
Cimetidine	100
Cimetidine.HNO ₃	50
Ranitidine	80
Ranitidine.HNO ₃	40

CLAIMS

1. Nitrate salts of one or more components selected from the following compound classes:



where in the (A) class compounds:

$R = H, OCH_3, OCHF_2;$

$R_1 = CH_3, OCH_3;$

$R_2 = H, CH_3;$

$R_3 = CH_3, CH_2-CF_3, (CH_2)_3-OCH_3;$

where in the (B) class compounds:

R_3^I, R_4^I equal to or different from each other, are respectively free valence, hydrogen, $-N=C(NH_2)_2$,

$-CH_2-N(CH_3)_2;$

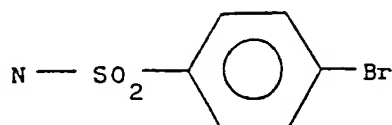
$Y = S, N-R_6^I, CR_7^I, R_8^I;$

$X = O, S, N-R^I_1;$

$R_2 = H, CH_3;$

$n = 0, 1;$

$Z = N-CN, N-SO_2NH_2, CH-NO_2$ or

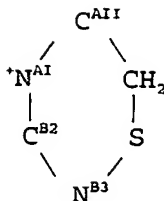


(VIIA)

$R^I_5 = H, -NH-CH_3, NH_2;$

$R^I_6, R^I_7, R^I_8, R^I_1$, equal or different from each other, are hydrogen, free valence.

2. Salts according to claim 1 where in the compounds of (A) formula $R = OCH_3$, $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = CH_3$, Omeprazole residue;
as in Omeprazole, but with $R = OCHF_2$, $R_1 = OCH_3$, $R_2 = H$,
Pantoprazole residue;
as in Omeprazole, but with $R = H$, $R_2 = H$, $R_3 = (CH_2)_3-OCH_3$,
Rabeprazole residue;
as in Rabeprazole, but with $R_3 = CH_2-CF_3$, Lansoprazole residue.
3. Salts according to claims 1 e 2 comprising (A) formula compounds having the following intramolecular ring, obtainable by treating the precursors in acid environment:



wherein N^{AI} e C^{AII} are, respectively, the nitrogen and carbon atom in 1 and 2 position of the pyridine ring and C^{B2} and N^{B3} the carbon and nitrogen atom, respectively, in 2 and 3 position of the imidazole ring.

4. Salts according to claim 1 where in (B) formula $X = N-R^I_1$ with R^I_1 free valence, $Y = N-R^I_6$ with $R^I_6 = H$, $R^I_3 = H$, R^I_4 is a free valence and forms with R^I_1 a double bond, $R^I_2 = CH_3$, $n = 1$, $R^I_5 = -NH-CH_3$, $Z = N-CN$, Cimetidine residue;

when in (B) formula $X = N-R^I_1$ with R^I_1 free valence, $Y = S$, $R^I_3 = -N=C(NH_2)_2$, R^I_4 is a free valence and forms with R^I_1 a double bond, $R^I_2 = H$, $n = 1$, $R^I_5 = H$, $Z = (VII_A)$, Ebrotidine residue;

as in Ebrotidine but with $n = 0$, $R^I_5 = NH_2$ and $Z = N-SO_2-NH_2$, Famotidine residue;

as in Ebrotidine but with $R^I_3 = -CH_2-N(CH_3)_2$, $R^I_5 = -NH-CH_3$ and $Z = CH-NO_2$, Nizatidine residue;

as in Nizatidine, but with $X = \text{oxygen}$, $Y = CR^I_7R^I_8$ with R^I_7 hydrogen and R^I_8 free valence, R^I_4 is a free valence and forms with R^I_1 a double bond, Ranitidine residue.

5. Nitrate salts according to claims 1-4, containing one or more isomers of the compounds belonging to (A) and (B)

classes.

6. Salts according to claims 1-5, wherein the compound salts of (A) and (B) classes contain at least one mole of nitrate ion/mole of compound.
7. Pharmaceutical compositions of nitrate salts according to claims 1-6.
8. Nitrate salts and pharmaceutical compositions according to claims 1-7 for use as medicament.
9. Use of the salt and composition according to claim 8 for the preparation of medicaments for the treatment of ulcers and gastric dyspepsias.
10. Use according to claims 8-9 wherein the salt and pharmaceutical composition dosages are the conventional ones of their (A) and (B) class precursors.
11. Compositions obtainable by combining one or more nitrate salts of (A) and (B) class compounds, or their pharmaceutical compositions, according to claims 1-10 with conventional gastroprotectives .
12. Compositions according to claim 11 wherein conventional gastroprotectives are selected from prostaglandins, bismuth salts and antibiotics.
13. Use of compositions according to claims 11-12 for preparing medicines for the therapy and prevention of ulcer and dyspepsia relapses.
14. Preparation process of nitrate salts according to claims from 1 to 6 wherein, when the substance to be salified is available as free base or as a soluble corresponding salt

in an organic solvent which does not contain hydroxyl groups the salt is prepared by dissolving the substance in the solvent at a concentration equal or higher than 10% w/v, by adding the amount of concentrated nitric acid corresponding to the moles of salifiable aminic groups present in the compound, by cooling during and after the addition at temperatures in the range 20°-0°C and by recovering the product by filtration.

15. Process according to claim 14 wherein when the substance is not much soluble or it is available as a not much soluble salt in the above mentioned solvent, the corresponding mixtures with hydroxylated solvents are used and the precipitation is quickened by diluting the so obtained mixture, after the addition of nitric acid, with an apolar solvent.
16. Process according to claims 14-15 wherein when the starting material is salified with hydrochloric acid, the salt with nitric acid is prepared by directly adding silver nitrate to the compound solution, by filtering the silver chloride; the solution is then concentrated and cooled to recover the nitric salt.
17. Process for the preparation of nitrate salts according to claims from 1 to 6 wherein when the starting product is a salt, the corresponding base is liberated by a treatment with a sodium or potassium carbonate or bicarbonate saturated solution or with a sodium or potassium hydroxide diluted solution, by extracting the

base with a suitable organic solvent and by following the methods to prepare the nitrate salt mentioned at the claims 14 or 15.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 99/01226

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D401/12 C07D233/61 C07D307/52 C07D277/28 C07D277/48
A61K31/44 A61K31/415 A61K31/34 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 285 681 A (HEUMANN PHARMA GMBH & CO) 12 October 1988 see page 5, line 33 - line 38; claims ---	1,4-17
X	DE 23 44 779 A (SMITH KLINE FRENCH LAB) 14 March 1974 see page 3; claims ---	1,4-17
X	EP 0 224 612 A (HEUMANN PHARMA GMBH & CO) 10 June 1987 see page 5, line 19 - line 21; claim 1 ---	1,4-17
X	EP 0 049 618 A (ELI LILLY AND COMPANY) 14 April 1982 see page 7, line 13 - line 23; claims --- -/--	1,4-17

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

1 June 1999

Date of mailing of the international search report

10/06/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Henry, J

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 99/01226

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 005 129 A (HAESSLE AB) 31 October 1979 see page 8, line 1-9; claims -----	1-3, 5-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/01226

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0285681 A	12-10-1988	AT 86619 T	15-03-1993
		AU 597159 B	24-05-1990
		AU 1313488 A	06-10-1988
		CA 1321594 A	24-08-1993
		DK 155488 A	07-10-1988
		GR 3007314 T	30-07-1993
		IE 61744 B	30-11-1994
		JP 2755385 B	20-05-1998
		JP 63258861 A	26-10-1988
		KR 9410179 B	22-10-1994
		PT 87116 A,B	01-04-1988
		US 4968808 A	06-11-1990
DE 2344779 A	14-03-1974	GB 1397436 A	11-06-1975
		AU 472456 B	27-05-1976
		AU 5890373 A	06-02-1975
		CA 1045142 A	26-12-1978
		CY 855 A	10-09-1976
		FR 2199467 A	12-04-1975
		HK 55276 A	17-09-1976
		IE 38353 B	01-03-1978
		JP 1062766 C	31-08-1981
		JP 49075574 A	20-07-1974
		JP 56001309 B	13-01-1981
		KE 2626 A	28-05-1976
		NL 7312198 A,C	07-03-1974
		US 3876647 A	08-04-1975
		US 3897444 A	29-07-1975
		US 3920822 A	18-11-1975
		US 3975530 A	17-08-1976
		BE 804144 A	28-02-1974
EP 0224612 A	10-06-1987	AU 583435 B	27-04-1989
		AU 6566286 A	11-06-1987
		DK 574086 A	06-06-1987
		GR 862829 A	07-04-1987
		JP 62138479 A	22-06-1987
		PT 83869 A,B	01-01-1987
EP 0049618 A	14-04-1982	US 4375547 A	01-03-1983
		AT 14879 T	15-08-1985
		AU 542553 B	28-02-1985
		AU 7594581 A	08-04-1982
		BG 60249 B	24-03-1994
		CA 1166248 A	24-04-1984
		CS 227015 B	16-04-1984
		CS 227049 B	16-04-1984
		CY 1351 A	24-04-1987
		DD 200371 A	20-04-1983
		DK 12391 A	24-01-1991
		DK 435181 A,B,	12-05-1982
		EG 15678 A	30-12-1986
		FI 813058 A	03-04-1982
		FI 76570 B	29-07-1988
		GB 2084581 A,B	15-04-1982
		GR 75023 A	12-07-1984
		HK 15987 A	27-02-1987
		IE 51603 B	21-01-1987

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/01226

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0049618 A		JP 1576444 C	24-08-1990
		JP 2001141 B	10-01-1990
		JP 57091980 A	08-06-1982
		KE 3680 A	30-04-1987
		LU 88293 A	04-05-1994
		MX 5723 A	01-12-1993
		PH 18135 A	03-04-1985
		PT 73757 A, B	01-11-1981
		SU 1184443 A	07-10-1985
		US 4904792 A	27-02-1990
		US 4382090 A	03-05-1983
		US 4760075 A	26-07-1988
		YU 236481 A	31-10-1983
		ZA 8106817 A	25-05-1983
EP 0005129 A	31-10-1979	AT 375365 B	25-07-1984
		AT 100583 A	15-12-1983
		AT 374472 B	25-04-1984
		AT 100683 A	15-09-1983
		AT 374473 B	25-04-1984
		AT 100783 A	15-09-1983
		AT 374471 B	25-04-1984
		AT 273279 A	15-09-1983
		AT 389995 B	26-02-1990
		AU 529654 B	16-06-1983
		AU 4602779 A	18-10-1979
		BG 61492 B	30-09-1997
		CA 1127158 A	06-07-1982
		CA 1129417 A	10-08-1982
		CS 7902549 A	15-07-1988
		CS 8405767 A	15-07-1988
		CS 8405768 A	15-07-1988
		CS 8405769 A	15-07-1988
		CY 1232 A	29-06-1984
		DD 142882 A	16-07-1980
		DK 151179 A, B,	15-10-1979
		DK 420982 A, B,	22-09-1982
		FI 791219 A, B,	15-10-1979
		FI 832220 A, B,	17-06-1983
		HK 15284 A	02-03-1984
		IE 48370 B	26-12-1984
		JP 1312930 C	28-04-1986
		JP 54141783 A	05-11-1979
		JP 60034956 B	12-08-1985
		JP 1504537 C	13-07-1989
		JP 58192880 A	10-11-1983
		JP 63053191 B	21-10-1988
		LT 2274 R	15-12-1993
		LT 2275 R	15-12-1993
		LT 2276 R	15-12-1993
		LT 2277 R	15-12-1993
		LU 88305 A	04-05-1994
		LU 88307 A	04-05-1994
		LV 5502 A	10-03-1994
		LV 5487 A	10-03-1994
		LV 5488 A	10-03-1994
		LV 5489 A	10-03-1994
		NZ 190203 A	16-03-1984

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int: onal Application No

PCT/EP 99/01226

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0005129 A		SE 7804231 A	15-10-1979
		SU 895292 A	30-12-1981
		US 4255431 A	10-03-1981
		US 4337257 A	29-06-1982
		US 4508905 A	02-04-1985
		ZA 7901586 A	30-04-1980

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.